ATHEROSCLEROSIS AND GARLIC (ALLIUM SATIVUM) ROLE IN ITS PREVENTION AND TREATMENT

Nino Qurashvili
PhD, Professor, University of Georgia,
School of Health Sciences,
Department of Pharmacy, Georgia

SUMMARY

Background. Cardiovascular disease is a universal problem in modern society. Atherosclerosis is the leading cause of cardiovascular disease resulting in high rate of mortality in the population. Atherosclerosis major clinical manifestations include ischemic heart disease, ischemic stroke, and peripheral arterial disease. It can lead to kidney problems, high blood pressure, stroke, and other life-threatening conditions. Non-traditional drivers of atherosclerosis-such as disturbed sleep, physical inactivity, the microbiome, air pollution and environmental stress have also gained attention. Some phytomedicines are useful in the prevention or symptomatic treatment of atherosclerosis and its sequelae. Particular value is ascribed to certain Allium species and among them, garlic.

Aim of research. Aim of our research was to obtain and analyse scientific data on atherosclerosis and garlic (allium sativum), focusing on the effect of the latter to reduce the risk of atherosclerosis. In addition, our objective was to collect all available data on side effects of garlic as well as to evaluate future research opportunities for this plant.

Methodology. Systematic literature and databases, both local and international, searches have been carried out and all relevant works assessed. The data were collected via electronic as well as library search for articles published in peer-reviewed journals. No restrictions regarding the language of publication were imposed. The authors reviewed articles and extracted data, with any disagreements resolved by consensus.

Results and discussion. Many studies have demonstrated the hypotensive, lipid-lowering, cholesterol-lowering, and age-related arterial changes progression slowing effects of garlic. Most of the medicinal effects of garlic are referable to the sulfur compounds and the alliin-splitting enzyme alliinase. Garlic, in an amount approximating one half to one clove per day, decreased total serum cholesterol levels by about 12%. Garlic extracts and several garlic constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. According to the team of scientists, garlic extract works exactly the same way, but two and a half times more potently, than HDL – cholsterol, inhibiting formation and accumulation of tiny plaques.

Although extensive scientific researches proved the efficacy of garlic preparations in prevention and symptomatic treatment of atherosclerosis, a number of case reports have reflected adverse effects of this plant and its preparations. Side effects of Garlic consumption include: a spontaneous spinal epidural haematoma associated with platelet dysfunction from excessive garlic ingestion; gastrointestinal discomfort and nausea; allergic skin reactions; allergic conjunctivitis, rhinitis, or bronchospasms occurring in response to garlic inhalation or ingestion; severe contact dermatitis. Ingested fresh garlic or garlic preparations may interact with anticoagulants or platelet aggregation inhibitors and potentiate its effect, leading in one case to a life-threatening hemorrhage.

Conclusion. Having studied the obtained materials closely, we concluded that fresh garlic, as well as garlic preparations, have the potential of prevention and treatment of atherosclerosis. However, further multidisciplinary research is desirable to exploit the plants potential further.

Keywords: Cardiovascular disease, atherosclerosis; cholesterol; garlic; Allium sativum.

ათეროსკლეროზი და ნივრის (ALLIUM SATIVUM) როლი მის პრევენციასა და მკურნალობაში

ნინო ყურაშვილი,
PhD, პროფესორი, საქართველოს უნივერსიტეტი,ჯანმრთელობის მეცნიერებების სკოლა, ფარმაციის დეპარტამენტი, საქართველო

რეზიუმე

კვლევის წინაპირობა. გულსისხლძარღვთა დაავადებები თანამედროვე საზოგადოების სერიოზულ პრობლემას წარმოადგენს. ამ დაავადებების მთავარი გამომწვევი მიზეზია ათეროსკლეროზი, რომელიც სიკვდილიანობის მაღალ მაჩვენებლებს განაპირობებს. ათეროსკლეროზის კლინიკური გამოვლინებებია: გულის იშემიური დაავადება, იშემიური ინსულტი და პერიფერული არტერიული დაავადება. ათეროსკლეროზი ასევე იწვევს თირკმლების დაავადებებს, მაღალ არტერიულ წნევას, ინსულტს

და სიცოცხლისთვის საშიშ სხვა გართულებებს. ათეროსკლეროზის გამომწვევი სხვა მიზეზები, როგორიცაა არასრულფასოვანი ძილი, ფიზიკური არააქტიურობა, მიკრობიომი, ჰაერის დაბინძურება და სტრესი, აგრეთვე, მოითხოვს განსაკუთრებულ ყურადრებას.

ზოგიერთი ფიტოპრეპარატი წარმატებით გამოიყენება ათეროსკლეროზის და მისი გართულებების პრევენციისა და სიმპტომური მკურნალობისთვის. განსაკუთრებულად ეფექტურია Allium-ის წამომადგენლები, მათ შორის, ნიორი.

კვლევის მიზანი. ჩვენი კვლევის მიზანს წარმოადგენდა ათეროსკლეროზსა და ნიორზე სამეცნიერო კვლევების მოპოვება, ანალიზი და ნივრის მოხმარების გავლენა ათეროსკლეროზის სიმპტომების შემცირებაზე. გარდა ამისა, ჩვენი მიზანი იყო ნიორის გამოყენების გვერდითი მოვლენების შესახებ ინფორმაციის შეკრება და ამ მცენარის შემდგომი კვლევის შესაძლებლობების გარკვევა.

მეთოდოლოგია. ჩატარდა როგორც ადგილობრივი, ისე საერთაშორისო სამეცნიერო ლიტერატურის და მონაცემთა ბაზების სისტემური კვლევა და ყველა შესაბამისი ნაშრომის შეფასება. სამეცნიერო ჟურნალებში დაბეჭდილი სტატიები მოვიპოვეთ როგორც ელექტრონულად, ისე ბიბლიოთეკებში. პუბლიკაციის ენაზე შეზღუდვები არ გვქონია. ავტორებმა შეისწავლეს სტატიები და შეაგროვეს მონაცემები; აზრთა სხვადასხვაობის შემთხვევაში, შეთანხმება მიიღწეოდა კონსესუსით.

მიღებული შედეგები: შესწავლილმა მასალამ გამოავლინა, რომ ნიორსა და მის პრეპარატებს გააჩნიათ ჰიპოტენზიური, ქოლესტერინისა და ლიპიდების შემამცირებელი და ასაკის მატებით გამოწვეული არტერიულის ცვლილებების შემანელებელი ეფექტი.

ნიორის სამკურნალო თვისებების უმეტესობა განპირობებულია მასში გოგირდისა ნაერთების არსებობით. დღეში ერთ კბილამდე ნიორის მოხმარება ქოლესტერინის დონეს ამცირებს 12 %-ით. ნივრის ექსტრაქტსა და მის რამდენიმე აქტიურ ნივთიერებას აქვს ანტითრომბული მოქმედება როგორც in vitro, ისე in vivo სისტემებში. მკვლევართა ერთი ჯგუფის მიხედვით, ნიორის ექსტრაქტი მოქმედებს იგივე შედეგით და ორჯერ უფრო ეფექტურად, ვიდრე მაღალი სიმკვრივი ლიპოპროტეინის ქოლერსტერინი, რითაც ხელს უშლის ათეროსკლეროზული მცირე ზომის ფოლაქების წარმოქმნასა და აგრეგაციას.

მიუხედავად იმისა, რომ სამეცნიერო კვლევებმა აჩვენა ნიორის პრეპარატების ეფექტურობა ათეროსკლეროზის პრევენციისა და სიმპტომური მკურნალობისთვის, რიგი კვლევისას გამოვლინდა ამ პრეპარატების გვერდითი მოვლენები,მათ შორის: ეპიდურალური ჰემატომა, გამოწვეული ნივრის ჭარბი მოხმარებით, გასტროინტესტინალური დისკომფორტი და გულისრევა, კანის ალერგიული რეაქციები, ალერგიული კონიუქტივიტი, რინიტი ან ბრონქოსპაზმი, მწვავე კონტაქტური დერმატიტი. ნიორის პრეპარატები შეიძლება რეაქციაში შევიდეს ანტიკოაგულანტებთან ან პლატელიტების აგრეგაციის ინჰიბიტორებთან და გააძლიეროს მათი მოქმედება, შედეგად, ვითარდება სიცოცხლესთან შეუთავსებელი ჰემორაგია.

დასკვნა: მოპოვებული მასალის შესწავლისას მივედით დასკვნამდე, რომ ნივრის პრეპარატებს გააჩნიათ ათეროსკლეროზის პრევენციისა და ეფექტური სიმპტომური მკურნალობის უნარი. მიუხედავად ამისა, საჭიროა შემდგომი მულტიდისციპლინარული კვლევა ამ მცენარის დამატებითი პოტენციალის გამოსავლენად.

საკვანძო სიტყვები: გულსისხლძარღვთა დაავადებები, ათეროსკლეროზი, ნიორი, Allium sativum.

INTRODUCTION

Cardiovascular disease (CVD) is a universal problem in modern society. Atherosclerosis is the leading cause of cardiovascular disease resulting in high rate of mortality in the world population. (Nimbe Torreset al., 2015).

The risk of developing atherosclerosis is no longer concentrated in Western countries, and it is instead involved in the majority of deaths worldwide. Atherosclerosis now affects younger people, and more women and individuals from a diverse range of ethnic backgrounds, than was formerly the case. The risk factor profile has shifted as levels of low-density lipoprotein (LDL) cholesterol, blood pressure and smoking have decreased. Recent research has challenged the protective effects of high-density lipoprotein, and now focuses on triglyceride-rich lipoproteins in addition to low-density lipoprotein as causal in atherosclerosis. Non-traditional drivers of atherosclerosis-such as disturbed sleep, physical inactivity, the microbiome, air pollution and environmental stress-have also gained attention (Libby, 2021).

Atherosclerosis major clinical manifestations include ischemic heart disease, ischemic stroke, and peripheral arterial disease. In high-income countries, there have been dramatic declines in the incidence and mortality from ischemic heart disease and ischemic stroke since the middle of the 20th century. For example, in the United Kingdom, the probability of death from vascular disease in middle-aged men (35-69 years) has decreased from 22% in 1950 to 6% in 2010. Most low- and middle-income countries have also reported declines in mortality from stroke over the last few decades, but mortality trends from ischemic heart

disease have been more varied, with some countries reporting declines and others reporting increases, particularly those in Eastern Europe and Asia (Herrington et al.,2016).

Some phytomedicines are useful in the prevention or symptomatic treatment of atherosclerosis and its sequelae. Particular value is ascribed to certain Allium species - garlic, onion, and ransom in the prevention of atherosclerosis, and the effects of garlic have been extensively documented by pharmacologic and clinical research.

METHODOLOGY.

Systematic literature and databases, both local and international, searches have been carried out and all relevant works assessed. The data were collected via electronic as well as library search for articles published in peer-reviewed journals. No restrictions regarding the language of publication were imposed. The authors reviewed articles and extracted data, with any disagreements resolved by consensus.

RESULTS AND DISCUSSION

Arteriosclerosis is a generic term for a number of diseases in which the arterial wall becomes thickened and loses elasticity. Atherosclerosis (AS) is a form of arteriosclerosis characterized by patchy subintimal thickening (atheromas) of medium and large arteries, which can reduce or obstruct blood flow.

The term arteriosclerosis refers to several diseases involving arteries of various sized and different layers of the arterial walls. From Greek words that means "hardening of the arteries," the term originally signified the tendency of arteries to become hard and brittle through the deposition of calcium in their walls. However, this is not an important characteristic of the most familiar form of arteriosclerosis, atherosclerosis. This disease is characterized by fatty deposits on the intima, or inner lining, of the arteries.

The presence of these fatty deposits, called arterial plaques, leads to an important loss of arterial elasticity and a narrowing of the artery. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood (Hoffman,2003). Clots may lodge in arteries supplying the heart, causing a heart attack, or the brain, causing stroke. Atherosclerosis may be manifested fairly rapidly in diseases in which the concentration of blood lipids is raised, such as diabetes (Schulz V. et al., 2004).

Depending on the location and degree of arterial damage, atherosclerosis can lead to kidney problems, high blood pressure, stroke, and other life-threatening conditions. Damage to the arteries that carry blood to the legs and feet can cause peripheral arterial occlusive disease, which makes walking painful. Severely restricted circulation to the limbs can also cause skin ulcers and even gangrene (tissue death).Blockage in the coronary arteries, which feed oxygen rich blood directly to the heart muscles, is known as coronary artery disease or coronary heart disease. Such blockage causes ischemia, a localized oxygen starvation affecting tissues.

Atherosclerotic deposits begin as thin, fatty streaks on an arterial wall. Such streaks may come and go in a person with a healthy lifestyle. However, if the arteries are damaged – typically, from high blood pressure, stress, or smoking, the inner surface of the walls can start to deteriorate. To compensate, the artery grows new tissue that may create tiny bumps or scars. Cholesterol, white blood cells, and other deposits can begin to accumulate within these bumps, forming plaques that clog the arteries. Eventually, calcium deposits and scar tissue surround the soft plaques, making the arteries hard and inelastic. Atherosclerosis progresses over many years, which perhaps contributes to the perception that it is an affliction of aging. However, it appears that arterial deposits can begin in childhood, with significant plaque formation by the time a person is 30 years old.

When plaque limits blood flow, it can cause a variety of problems. Peripheral artery disease (PAD) can cause leg pain when walking or abdominal pain after eating. Severe PAD can lead to foot or leg amputation. Because of the atherosclerosis connection, many people with PAD die from a heart attack, sudden cardiac arrest, or stroke (Hoffman,2003).

To the symptoms of peripheral arterial occlusive disease belong painful cramping in one or both of hips, thighs or calf muscles after certain activities, such as walking or climbing stairs (claudication), leg numbness or weakness, coldness in the lower leg or foot, especially when compared with the other side.

A number of biochemical, physiological, and environmental risk factors increase the chance that an individual will develop atherosclerosis:

1. Hypertension. High blood pressure is a critical factor in the atherosclerotic process, which does not normally occur in low-pressure pulmonary arteries and veins, despite the fact that they are bathed by the same blood concentration of lipids.

2. Elevated serum lipid levels. The atherogenicity of cholesterol is influenced by type of lipoprotein. LDL is clearly atherogenic, but HDL appears to prevent accumulation of cholesterol in the tissues.

3. Obesity promotes the development of all risk factors.

4. Cigarette smoking increases the chance of developing this and many other diseases.

5. Diet rich in saturated fats, cholesterol, and calories appear to be chiefly responsible for high blood cholesterol, and such diets are therefore believed to promote atheroscleroses.

6. Family history of premature atherosclerotic disease appears to indicate either a propensity to higher levels of LDL or an increased susceptibility to atherosclerosis risk factors. Inborn errors in lipid metabolism also increase susceptibility.

7. Gender. Between the ages of 35 and 44, the death rate from coronary heart disease among white men is 6.1 times that for white women.

8. Aging bringgs about degenerative arterial changes such as dilation, tortuousness, thickening, and loss of elasticity.

9. Lifestyle factors, including diet and stress level, can contribute.

Some phytomedicines are useful in the prevention or symptomatic treatment of atherosclerosis and its sequelae. Particular value is ascribed to certain Allium species - garlic, onion, and ransom in the prevention of atherosclerosis, and the effects of garlic have been extensively documented by pharmacologic and clinical research.

The antiatherosclerotic effects of garlic are based mainly on its vasodilating, rheologic, and lipid-reducing actions. It has been discovered that garlic lowers blood lipids by inhibiting cholesterol synthesis. Some of the earliest references about garlic are found on Sumerian clay tablets dating from 2600-2100 BC. Garlic was an important medicine to the ancient Egyptians appearing in 22 of the more than 800 remedies listed in the famous ancient papyrus (1550 BC).

Garlic has been known in Europe as a healing herb since the Middle Ages. It owed much of its popularity to the Benedictine monks who grew garlic in their monastery gardens. Garlic was thought to be a valuable remedy for communicable diseases, and many references are found to its use in plagues. When Basel was struck by the plague, the Jewish population who consumed the garlic regularly, fared much better than other citizens. In 1721 during the plague time in Marseilles, a band of thieves was robbing the sick and dead alike without contracting the disease themselves. When one of the thieves was caught, he explained that this band had regularly consumed garlic soaked in wine and vinegar.

Garlic cloves, seeds and flowers were mentioned in ancient Georgian medical manuscripts as remedies for severe headaches, weakness and fungi healing. Iadigar daudi (XVI century) says “Who eats garlic will be healed from tumors” and Karabadini (Book of Medical Treatment, XV century) by Zaza Panaskerteli teaches “Where there is fungi on the head, a healer should cut off hair and then rub the head with garlic, vinegar, and salt.” (Iosebidze, 2022). However, we could not find any evidence that garlic was used as an anti atherosclerosis remedy in medieval centuries. Perhaps that was because the term of “atherosclerosis” was not used those days. But in Georgian falk medicine of last century, garlic was already used for treating hypertension and atherosclerosis. (Mamatsashvili, 2022).

Besides its antimicrobial properties, garlic was prized by the peoples of Europe for its effects on the heart and blood circulation. For example, garlic was commonly recommended as a remedy for “dropsy” (cardiac insufficiency)(Koch et al.,1996).

Garlic (Allium sativum) is a species of bulbous flowering plant in the genus Allium. Its close relatives include the onion, shallot, leek, chive, Welsh onion, and Chinese onion. It is native to South Asia, Central Asia and northeastern Iran and has long been used as a seasoning worldwide, with a history of several thousand years of human consumption and use. It was known to ancient Egyptians and has been used as both a food flavoring and a traditional medicine. China produces 76% of the world’s supply of garlic (Block, 2010). The word garlic derives from Old English meaning gar (spear) and leek, as a ‘spear-shaped leek’ (Douglas, 2018).

Allium sativum is a perennial flowering plant that grows from a bulb. It has a tall, erect flowering stem that grows up to 1 m. The leaf blade is flat, linear, solid, and approximately 1.25–2.5 cm wide, with an acute apex. The plant may produce pink to purple flowers from July to September in the Northern Hemisphere. The bulb has a strong odor and is typically made up of 10 to 20 cloves. The cloves close to the center are symmetrical, and those surrounding the center can be asymmetrical. Each clove is enclosed in an inner sheathing leaf surrounded by layers of outer sheathing leaves.

The constituents of garlic are ordinarily divided into two groups: sulfur-containing and non-sulfur-containing compounds. Most of the medicinal effects of garlic are referable to the sulfur compounds and the alliin-splitting enzyme alliinase. Thus, commercial garlic preparations are often adjusted or standardized to sulfur-containing ingredients, particularly to the amino acid alliin contained in garlic powder. When the garlic bulb is chopped and crushed, damage to the cells allows the aliin to come into contact with alliinase, and within minutes, the enzyme converts the aliin into the volatile compound allicin. Allicin has an aromatic odor but is unstable in aqueous and oily solutions, and within a few hours it degrades into vinyldithiins and ajoene. Cold oil infusions and distilled garlic oils contain only the products of aliin degradation. (Schulz,2004).

Allium sativum is complex and the multitude of garlic products are available in the marketplace. These types of preparations can be divided into three main groups, to which is added fresh garlic:

1. Carefully dried *garlic powder* that preserves the compound alliin (S-allylcysteine sulphoxide) and the enzyme alliinase. On disintegration of tablets or capsules containing this powder in the digestive tract, alliin comes into contact with alliinase and is converted to allicin. This must take place outside the stomach, as gastric acid inhibits alliinase. Enteric coating of the tablets or capsules is therefore necessary. Allicin is unstable and breaks down further into compounds such as diallyl sulphides, ajoene and the vinyl dithiins.

2. *Aged garlic extracts* or 'odorless' garlic products that are produced by a fermentation process. These preparations contain modified sulphur compounds such as S-allylcysteine.

3. *Steam-distilled preparations of garlic* (garlic oil) rich in diallyl sulphides.

Most of the published clinical studies on garlic have used 'garlic powder' preparations, although trials on aged garlic extracts, fresh garlic and garlic oil are also in the literature (Sendl,1995).

Garlic oil is typically prepared using steam distillation, where crushed garlic is steamed with the resultant condensation containing the oil. Garlic oil contains volatile sulfur compounds such as diallyl disulfide, a 60% constituent of the oil. Garlic oil is typically prepared using steam distillation, where crushed garlic is steamed with the resultant condensation containing the oil. Garlic oil contains volatile sulfur compounds such as diallyl disulfide, a 60% constituent of the oil.

Many studies have demonstrated the lipid-lowering effects of garlic and the results of meta-analyses have supported the premise that garlic acts as a lipid-lowering agent. One examined five selected clinical trials on various garlic preparations with a total of 410 patients (Warshafsky, 1993). The authors concluded that

the best available evidence suggests that garlic, in an amount approximating one half to one clove per day, decreased total serum cholesterol levels by about 9%. About a year later a second meta-analysis was published by Silagy and Neil (Silagy, 1994). These scientists included 16 clinical trials with a total of 952 patients. Again, a variety of garlic preparations were included in the meta-analysis. They found that garlic lowered cholesterol levels by 12% and that dried garlic powder preparations also lowered serum levels of triglycerides.

Most studies on garlic during the past 15 years have been primarily in the fields of cardiovascular and cancer research. Cardiovascular studies have been mainly related to atherosclerosis, where effects were examined on serum cholesterol, LDL, HDL, and triglycerides. Although the studies were not consistent in relation to the dosage, standardization of garlic preparations, and period of treatment, most findings suggest that garlic decreases cholesterol and triglycerides levels in patients with increased levels of these lipids. Lowering of serum lipids by garlic ingestion may decrease the atherosclerosis process. The other major beneficial effect of garlic is due to its antithrombotic actions. Garlic extracts and several garlic constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. Allicin and adenosine are the most potent antiplatelet constituents of garlic because of their in vitro effects. Only a small amount of ajoene can be found in garlic oil-macerates; however, ajoene is being developed as a drug for treatment of thromboembolic disorders. Recent findings on the identification of potent enzyme inhibiting activities of adenosine deaminase and cyclic AMP phosphodiesterase in garlic extracts may have a significant role in the pharmacological actions in the body. Presence of such enzyme inhibitors in garlic may perhaps explain several clinical effects in the body, including the antithrombotic, vasodilatory, and anticancer actions(Agarwal,1996).

Researchers reported that the hypotensive and cholesterol-lowering effects were investigated in two studies in men with mild arterial hypertension and in men with mild hypercholesterolemia. Eight-week treatment resulted in the reduction of both systolic and diastolic blood pressure by 5.2% (P=0.008) and 4.0% (P=0.014), respectively. In hypolipidemic study, the 12-week treatment resulted in a decrease in LDL cholesterol by 11.8% (P=0.002), while HDL cholesterol increased by 11.5% (P=0.013). In men with cerebral atherosclerosis it has been demonstrated that 14-days treatment inhibited ADP-induced platelet aggregation by 25.4% (P<0.05) and increased plasma fibrinolytic activity by 22.4% (P<0.05). One more study was performed in high-risk patients to evaluate the changes of prognostic cardiovascular risk that was calculated using algorithms derived from Framingham and Muenster Studies. Twelve-months treatment lowered 10-years prognostic risk of CHD by 13.2% in men (P=0.005), and by 7.1% in women (P=0.040). Ten-year prognostic risk of acute myocardial infarction and sudden coronary death was lowered by 26.1% in men (P=0.025). The Atherosclerosis Monitoring and Atherogenicity Reduction Study (AMAR) was designed to estimate the effect of two-year treatment with garlic powder pills on the progression of carotid atherosclerosis in asymptomatic men. A significant correlation has been revealed between the changes in blood serum atherogenicity and the changes in carotid intima-media thickness (r=0.144, P=0.045). Evidence obtained from these studies as well as series of double-blinded placebo-controlled clinical trials indicates that garlic powder pills are effective for prevention of cardiovascular disorders (Karagodin,2016).

A double blind, placebo-controlled study on 23 patients found that garlic powder tablets reduced the atherogenicity of low density lipoprotein. In a controlled retrospective study on 202 healthy adults, divided equally between those taking garlic powder and controls, in which measures of the elastic properties of the aorta were used, garlic reduced age-related increases in aortic stiffness (Breithaupt-Grogler,1997).

An important trial looked at the effect of garlic powder intake over 4 years on arterial plaque. The trial was a randomised, double blind, placebo-controlled design involving 152 patients (Schiermeier, 1999). Plaque volumes in both carotid and femoral arteries were measured by ultrasound. The increase in plaque volume over time was signifcantly reduced by garlic and in some cases there was a slight regression. The authors were accused of scientifc fraud, but subsequently vindicated (Koscielny,1999), (Koscielny,2000).

Researchers from Germany report that, in test tubes, garlic prevents formation of 'nanoplaques' that can accumulate to cause arteriosclerosis. During a National Institutes of Health workshop on herbs and cardiovascular disease held in Bethesda, MD, in August 2002, Dr Günter Siegel from the Free University of Berlin, described his team's research, which pinpoints exactly how garlic blunts plaque formation (Vastag,2002). In the presence of calcium, low-density lipoprotein (LDL)-cholesterol binds with molecules secreted from the inner lining of the arteries, forming tiny plaques that can accumulate and harden. HDL-cholesterol inhibits this process by absorbing excess plaque-forming molecules. Siegel's team found that garlic extract works exactly the same way, but more potently. Garlic extract was two and a half times more effective in inhibiting plaque formation than was HDL cholesterol (Vastag,2002). This has led to Siegel describing this form of garlic as phyto-HDL, that is a herb acting in the same benefcial way as HDL.

According to Orekhov and Grünwald (1997) garlic and garlic preparations can be used as agents for prevention and treatment of atherosclerosis and atherosclerosis-related diseases. Garlic indirectly effects atherosclerosis by reduction of hyperlipidemia, hypertension, and probably diabetes mellitus and prevents thrombus formation. In addition, in animal models, garlic causes direct antiatherogenic (preventive) and antiatherosclerotic (causing regression) effects at the level of artery wall. Garlic's direct effect on atherosclerosis may be explained by its capacity to reduce lipid content in arterial cells and to prevent intracellular lipid accumulation. This effect, in turn, is accompanied by other atherosclerotic manifestations, i.e., stimulation of cell proliferation and extracellular matrix synthesis. Clinical trials are currently being carried out to reveal the possible effect of garlic therapy on human atherosclerosis. Positive results of these trials may open a new era in the use of garlic for prevention and treatment of many atherosclerosis-related diseases (Orekhov,1997).

To evaluate whether aged garlic extract (AGE) can influence coronary artery calcification (CAC) and to predict the individual effect of AGE, a single-center parallel randomized controlled study has been conducted in a university hospital in Europe. Patients were randomized, in a double-blind manner, through a computer-generated randomization chart. Patients with a Framingham risk score ≥ 10 after CT scan (n = 104) were randomized to an intake of placebo or aged garlic extract (AGE) (2400 mg daily) for 1 year. Main outcome measures were changes in coronary artery calcification (CAC) score and secondary outcome measures changes in blood pressure, fasting blood glucose, blood lipids and inflammatory biomarkers. 104 patients were randomized and 46 in the active group and 47 in the placebo group were analyzed. There was a significant ($p < 0.05$) change in CAC progression (OR: 2.95 [1.05-8.27]), blood glucose (OR: 3.1 [1.09-8.85]) and IL-6 (OR 2.56 [1.00-6.53]) in favor of the active group. There was also a significant ($p = 0.027$) decrease in systolic blood pressure in the AGE group, from a mean of 148 (SD: 19) mmHg at 0 months, to 140 (SD: 15) mmHg after 12 months. The AGE Algorithm, at a selected probability cut-off value of 0.5, the accuracy score for CAC progression was 80%, precision score of 79% and recall score 83%. The score for blood pressure was 74% (accuracy, precision and recall). There were no side-effects in either group.

Authors of the study conclude that AGE inhibits CAC progression, lowers IL-6, glucose levels and blood pressure in patients at increased risk of cardiovascular events in a European cohort. An algorithm was made and was used to predict with 80% precision which patient will have a significantly reduced CAC progression using AGE. The algorithm could also predict with a 74% precision which patient will have a significant blood pressure lowering effect pressure using AGE (Wlosinska et al.,2020).

Although extensive scientific researched proved the efficacy of garlic preparations in prevention and treatment of atherosclerosis, a number of case reports have reflected adverse effects of garlic on bleeding parameters. A spontaneous spinal epidural haematoma associated with platelet dysfunction from excessive garlic ingestion was reported (Rose,1990). A patient taking garlic prior to cosmetic surgery experienced bleeding complications and had a clotting time of 12.5 minutes. After cessation of garlic, her clotting time dropped to 6 minutes and there were no complications during a second procedure (Burnham,1995).

The value of garlic as a prevention and treatment for cardiovascular diseases will best be determined by controlled clinical trials using cardiovascular morbidity or mortality as endpoints. In the meantime, garlic can be prescribed on the basis that it does favourably influence haemorheological parameters (blood flow characteristics) and some cardiovascular risk factors, including modest effect on serum cholesterol and blood pressure. Attention should be paid to the type of garlic preparation used; the strongest published evidence to date is for garlic powder preparations, although other preparations will also be of value. Caution should be exercised when prescribing garlic to patients who are also taking other blood-thinning medications such as aspirin or warfarin and garlic intake should be discontinued 10 days before surgery. However, a clinical trial with healthy volunteers found no adverse effect for garlic powder (enteric-coated standardized tablets, equivalent 4g/day of fresh garlic) taken with warfarin (Mohammed,2008).

Relatively few side effects were reported in the 30 treatment studies and 8 clinical pharmacologic studies using garlic powder preparations. Gastrointestinal discomfort and nausea were the most frequent comlaints. Reports of allergic skin reactions apparently represent a more specific response (Koch, 1996). There have also been sporadic reports of allergic conjunctivitis, rhinitis, or bronchospasms occurring in response to garlic inhalation or ingestion (Falleroni et al.,1981; Papageorgiou et al.,1983). Other cases of severe contact dermatitis have been reported (Emig et al, 1999).

From1990 to 1995, a total of four studies were published on how ingested fresh garlic or garlic preparations may interact with anticoagulants or platelet aggregation inhibitors (Rose et al., 1990; Sunter,1991; Burnham,1995; Petry,1995). All these studies found that garlic potentiated the anticoagulant effect, leading in one case to a life-threatening hemorrhage.

As the great majority of studies have been done with garlic powder tablets, the approval of garlic products for atherosclerosis prevention will cover only that type of product. The dosage in most studies was 600-900 mg per day, which is roughly equivalent to ingesting 2400-3700 mg of fresh garlic. The average daily dose recommended is equivalent to 4 g of fresh garlic clove.

With their overall pharmacodynamic and clinical profile, garlic powder tablets are able to slow the progression of age-related arterial changes and should therefore be classified as typical atherosclerosis remedies (Schulz, 2004).

CONCLUSION

1. Although the term "atherosclerosis" was not used by European people, since the middle ages, garlic was praised for its effects on the heart and blood circulation and was commonly recommended as a remedy for "dropsy" (cardiac insufficiency).

2. Garlic indirectly effects atherosclerosis by reduction of hyperlipidemia, hypertension, and probably diabetes mellitus and prevents thrombus formation.

3. According to Schulz and his team of researchers, garlic powder tablets are able to slow the progression of age-related arterial changes and should therefore be classified as typical atherosclerosis remedies.

4. Over the last 15 year scientific findings suggest that Garlic (Allium sativum) powder tablets, aged garlic extract, and garlic oil inhibit cholesterol synthesis, decrease cholesterol and triglycerides levels, lower blood lipids and thus, prevent atherosclerosis and its sequelae.

5. Most of the medicinal effects of garlic are referable to the sulfur compounds and the alliin-splitting enzyme alliinase. Garlic, in an amount approximating one half to one clove per day, decreased total serum cholesterol levels by about 12%.

6. Garlic extracts and its several constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. Allicin and adenosine are the most potent antiplatelet constituents.

7. According to Siegel's team of scientists, garlic extract works exactly the same way, but two and a half times more potently, than HDL – cholsterol, inhibiting formation and accumulation of tiny plaques.

8. Wlosinska and her team conclude that AGE inhibits CAC progression, lowers IL-6, glucose levels and blood pressure in patients at increased risk of cardiovascular events.

9. Side effects of Garlic consumption include: a spontaneous spinal epidural haematoma associated with platelet dysfunction from excessive garlic ingestion; gastrointestinal discomfort and nausea; allergic skin reactions; allergic conjunctivitis, rhinitis, or bronchospasms occurring in response to garlic inhalation or ingestion; severe contact dermatitis.

10. Ingested fresh garlic or garlic preparations may interact with anticoagulants or platelet aggregation inhibitors and potentiate its effect, leading in one case to a life-threatening hemorrhage.

11. The dosage for prevention and symptomatic treatment of atherosclerosis in most studies was 600-900 mg per day, which is roughly equivalent to ingesting 2400-3700 mg of fresh garlic. The average daily dose recommended is equivalent to 4 g of fresh garlic clove.

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Abbreviations: *CVD- Cardiovascular disease, PAD - Peripheral artery disease, AGE - aged garlic extract, CAC - coronary artery calcification, LDL - low-density lipoprotein, HDL-high-density lipoprotein, CRP-C-reactive protein.*